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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (c).

Docket Number	117-298	Type a plus sign (+) inside this box→	+

INVENTOR(S)/APPLICANT(S)

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TITLE OF THE INVENTION (280 characters)

PROCESS FOR QUALITY CONTROL OF MEDICINAL PLANT PRODUCTS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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[X]	A check or money order is enclosed to cover the Provisional filing fees ($150.00)/($75)	PROVISIONAL FILING FEE AMOUNT ($) 150.00
[ ]	The commissioner is hereby authorized to charge filing fees and credit Deposit Account Number 14-1140	

The invention was made by an agency of the United States Government or under a contact with an agency of the United States Government.

[X] No.

[ ] Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,
SIGNATURE _____ DATE August 19, 1999

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REGISTRATION NO. *(if appropriate)* 25,327

[ ] Additional inventors are being named on separately numbered sheets attached hereto.

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U.S. PATENT APPLICATION

Inventor(s): Peter HYLANDS

Invention: PROCESS FOR QUALITY CONTROL OF MEDICINAL PLANT PRODUCTS

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SPECIFICATION

N.77018

SPECIFICATION

FOR

PATENT APPLICATION

IN

UNITED STATES OF AMERICA

in the name of *Peter Hylands*, Laundry Cottage, Yewleigh Lane,

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PROCESS FOR QUALITY CONTROL OF MEDICINAL PLANT PRODUCTS

The present invention relates to the quality control of medicinal and nutritional substances derived from plants. In particular the invention relates to a process for producing a plant based medicinal or nutritional substance which satisfies a pre-defined pharmaceutical grade standard and which can therefore be licensed by drug regulatory authorities as a pharmaceutical product. The invention also allows the origin or quality of a plant based material to be determined by comparison with a standard, thereby providing a means for the standardisation, quality control, tracking and audit of such materials.

Many societies around the world have developed, through the centuries, a system of traditional medicine relying largely on the use of plants and herbs as therapeutic substances. Studies into the structures of the isolated active ingredients of these substances led to the chemical phase of drug discovery in the early and middle twentieth century. As a result some important drugs were developed which owe their origin to the empirical use of plants in traditional medicine.

In recent years there has been a significant growth of interest amongst the general public in the direct use of plants and plant extracts as health modifying agents, for instance ginseng, garlic, *Ginkgo biloba*, *Hypericum* (St John's wort), *Echinacea* and *Aloe Vera*. These are currently available on the market as herbal products and dietary supplements and annual sales of these products worldwide are currently in excess of £10 billion. In spite of this marketing potential the mainstream pharmaceutical industry has not so far directed its attention to the development of medicinal products derived from plants. This is due in part to problems associated with the complex nature and inherent non-uniformity of plant materials, including the lack of an established system by which drug regulatory approval for such products can be secured.

The materials used in herbal and plant based medicine are usually whole plants, parts of plants or plant extracts. Since plant materials contain many different chemical components the materials are, by definition, complex mixtures. This makes it very difficult to standardize and control the quality of the materials. Furthermore,

plants used in the practice of herbal medicine are frequently unavailable locally and therefore need to be obtained from sources which are remote from the end user. However, the supply of such plants from remote locations can be erratic and inaccurate, particularly because no detailed monographs (identity and quality standards) exist for the plants. The complex mixture of ingredients found in medicinal plants will in any event vary widely in type and concentration depending on many factors including the botanical origin, the location where the plant is grown, the time or year when the plant is harvested and the extraction procedure used.

As a consequence it is virtually impossible to provide any assurance that samples of a given plant material obtained from disparate sources will possess a uniform identity and biological activity. This inherent variability of plant materials presents a problem to the drug regulatory authorities who need to be convinced that a candidate product for pharmaceutical licencing is of a consistent and verifiable quality. This is so that, for instance, the effectiveness of dosage levels and treatment protocols can be guaranteed. However, there is no reliable system available at present which both allows the identity and activity of a plant based product to be measured against an accepted standard and is universally applicable to all kinds of plant material.

The present invention addresses this problem and, in one aspect, provides a process for producing a pharmaceutical grade therapeutic substance which is derived from, or consists of, a plant material, the process comprising:

(i) providing a test sample of the therapeutic substance in the form of a solution or extract;

(ii) submitting the test sample to high resolution NMR to generate an NMR fingerprint;

(iii) determining whether the NMR fingerprint generated in step (ii) matches that of a pre-determined pharmaceutical quality standard sample; and

(iv) selecting the therapeutic substance as being of pharmaceutical grade only if the NMR fingerprint matches that of the said standard sample.

The invention thus resides in the application of high resolution NMR techniques to the characterisation and/or standardisation of a plant-derived substance. The substance can be accepted or rejected depending on whether its NMR fingerprint matches that of a pre-determined pharmaceutical grade standard.

The high resolution NMR fingerprinting technique typically comprises:

(i) submitting the test sample to high field proton NMR and recording one or more NMR spectra;

(ii) evaluating the data obtained from the or each NMR spectrum by one or more computer-based pattern recognition procedures to obtain an NMR fingerprint of the sample; and

(iii) determining the presence or absence of marker features in the fingerprint which have been previously identified in the NMR fingerprint of a pharmaceutical quality standard sample.

The high resolution NMR fingerprinting technique thus involves a combination of ^1H NMR at high fields and computer based pattern recognition procedures. The NMR spectra are typically measured at 400 to 700 MHz, and the data derived from them are analysed by computer programs using techniques such as non-linear mapping and principal component analysis. Examples of the high resolution NMR fingerprinting technique are discussed by M. L. Anthony *et al* in Biomarkers 1996, 1, 35- 43 and Molecular Pharmacology 46, 199- 211, 1994, and by J.O.T. Gibb *et al* in Comp. Biochem. Physiol. vol. 118B No. 3, pp 587- 598, 1997.

An important advantage of this NMR technique is that it is not limited by a selective delivery or detection system. Spectra are recorded without prior purification of the test sample, thus allowing all components of the sample to contribute to the overall NMR "fingerprint". Analysis by the pattern recognition procedures as discussed above reveals potential valuable marker features of the spectra which can be used with a high degree of precision in the characterisation of the complex mixtures of components contained in plant materials.

In the process of the invention the therapeutic substance typically consists of, or is derived from, a whole plant, a part of a plant, a plant extract or a plant fraction. Preferably the substance consists of, or is derived from, one or more of the roots, leaves, buds, flowers, fruit, juice and seeds of a plant.

The process of the invention as described above relies upon the prior establishment of a pharmaceutical grade quality standard for the therapeutic substance in question, which is submitted to high resolution NMR to yield a characteristic NMR fingerprint. The pharmaceutical grade quality standard for a therapeutic substance which is derived from, or consists of, a plant material may therefore be provided by a process comprising:

(i) providing a test sample of the therapeutic substance, of the quality desired for the standard, in the form of a solution or extract;

(ii) submitting the test sample to high resolution NMR to generate an NMR fingerprint; and

(iii) defining the NMR fingerprint obtained in step (ii) as the standard to be met by any sample of the substance which is to be recognised as being of the desired pharmaceutical grade quality.

In another aspect the present invention further provides a process for determining whether a nutritional or therapeutic substance which derives from, or consists of, a plant material, has a specified origin or a desired quality, the process comprising:

(i) providing a test sample of the substance in the form of a solution or extract;

(ii) submitting the test sample to high resolution NMR to generate an NMR fingerprint;

(iii) determining whether the NMR fingerprint matches that of a previously tested standard sample having the specified origin or desired quality in question; and

(iv) selecting the substance as being of the specified origin or desired quality only if the NMR fingerprint matches that of the said standard sample.

CLAIMS

1. A process for producing a pharmaceutical grade therapeutic substance which is derived from, or consists of, a plant material, the process comprising:

(i) providing a test sample of the therapeutic substance in the form of a solution or extract;

(ii) submitting the test sample to high resolution NMR to generate an NMR fingerprint;

(iii) determining whether the NMR fingerprint generated in step (ii) matches that of a pre-determined pharmaceutical quality standard sample; and

(iv) selecting the therapeutic substance as being of pharmaceutical grade only if the NMR fingerprint matches that of the said standard sample.

2. A process according to claim 1 wherein the high resolution NMR technique comprises:

(i) submitting the test sample to high field proton NMR and recording one or more NMR spectra;

(ii) evaluating the data obtained from the or each NMR spectrum by one or more computer-based pattern recognition procedures to obtain an NMR fingerprint of the sample; and

(iii) determining the presence or absence of marker features in the fingerprint which have been previously identified in the NMR fingerprint of a pharmaceutical quality standard sample.

3. A process according to claim 2 wherein the computer-based pattern recognition procedures include non-linear mapping, principal component analysis and cluster analysis.

4. A process according to any one of the preceding claims wherein the therapeutic substance consists of, or is derived from, a whole plant, a part of a plant, a plant extract or a plant fraction.

5. A process according to any one of the preceding claims wherein the therapeutic substance consists of, or is derived from, one or more of the roots, leaves, buds, flowers, fruit, juice and seeds of a plant.

6. A pharmaceutical grade therapeutic substance produced by a process as claimed in any one of claims 1 to 5.

7. A process for determining whether a nutritional or therapeutic substance which derives from, or consists of, a plant material, has a specified origin or a desired quality, the process comprising:

(i) providing a test sample of the substance in the form of a solution or extract;

(ii) submitting the test sample to high resolution NMR to generate an NMR fingerprint;

(iii) determining whether the NMR fingerprint matches that of a previously tested standard sample having the specified origin or desired quality in question; and

(iv) selecting the substance as being of the specified origin or desired quality only if the NMR fingerprint matches that of the said standard sample.

8. A process according to claim 7 wherein the high resolution NMR technique comprises:

(i) submitting the test sample to high field proton NMR and recording one or more NMR spectra;

(ii) evaluating the data obtained from the or each NMR spectrum by one or more computer-based pattern recognition procedures to obtain an NMR fingerprint of the sample; and

(iii) determining the presence or absence of marker features in the fingerprint which have been previously identified in the NMR fingerprint of the standard sample.

9. A process according to claim 8 wherein the computer-based pattern recognition procedures include non-linear mapping, principal component analysis and cluster analysis.

10. A process according to any one of claims 7 to 9 wherein the nutritional or therapeutic substance consists of, or is derived from, a whole plant, a part of a plant, a plant extract or a plant fraction.

11. A process according to any one of claims 7 to 10 wherein the therapeutic substance consists of, or is derived from, one or more of the roots, leaves, buds, flowers, fruit, juice and seeds of a plant.

12.. A process for providing a pharmaceutical grade quality standard for a therapeutic substance which is derived from, or consists of, a plant material, the process comprising:

(i) providing a test sample of the therapeutic substance, of the quality desired for the standard, in the form of a solution or extract;

(ii) submitting the test sample to high resolution NMR to generate an NMR fingerprint; and

(iii) defining the NMR fingerprint obtained in step (ii) as the standard to be met by any sample of the substance which is to be recognised as being of the desired pharmaceutical grade quality.

ABSTRACT

PROCESS FOR QUALITY CONTROL OF MEDICINAL PLANT PRODUCTS

A process for producing a pharmaceutical grade therapeutic substance which is derived from, or consists of, a plant material, the process comprising:

(i) providing a test sample of the therapeutic substance in the form of a solution or extract;

(ii) submitting the test sample to high resolution NMR to generate an NMR fingerprint;

(iii) determining whether the NMR fingerprint generated in step (ii) matches that of a pre-determined pharmaceutical quality standard sample; and

(iv) selecting the therapeutic substance as being of pharmaceutical grade only if the NMR fingerprint matches that of the said standard sample.

The invention thus provides a means for the quality control of medicinal plant products and thereby overcomes problems associated with the inherently complex nature and variable quality of plant materials.